Impact of Sarilumab on Unacceptable Pain and Inflammation Control in Moderately-to-Severely Active Rheumatoid Arthritis Patients in 3 Phase 3 Studies

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INTRODUCTION

- High unacceptable levels of nociceptive pain can persist as a result of ongoing inflammation in the joint
  - Unacceptable levels of pain may also be present due to other mechanisms, and persist despite inflammation control induced via RA treatment (i.e. refractory pain) and if this were the case, would be observed in patients despite inflammation control
- Evidence is accumulating indicating that IL-6 contributes to pathological pain through unique downstream molecular and cellular mechanisms, suggesting that targeting IL-6 in patients with persistent unacceptable pain may offer therapeutic benefits[1]
- Sarilumab is a subcutaneously administered antagonist indicated for the treatment of adults with moderately-to-severely active RA with an inadequate response or intolerance to one or more conventional synthetic disease-modifying antirheumatic drugs (csDMARDs) or tumor necrosis factor inhibitors (TNFi)
- In Phase 3 randomized controlled trials (RCTs) of sarilumab, TARGET,[2] MOBILITY,[3] and MONARCH,[4] meaningful improvements in pain were demonstrated for sarilumab 150 mg or 200 mg every 2 weeks (Q2W) versus comparators, with an acceptable safety profile

OBJECTIVES

- This study assessed unacceptable pain and refractory pain despite inflammation control for sarilumab versus comparators in three Phase 3 RCTs

METHODS

Study design

- Patient data were from two RCTs of sarilumab 150 mg and 200 mg Q2W versus placebo added to conventional DMARDs, MOBILITY [NCT01061736] (24/52 weeks) and TARGET [NCT01709578] (24 weeks), and one RCT of sarilumab [NCT02332590] (24 weeks)

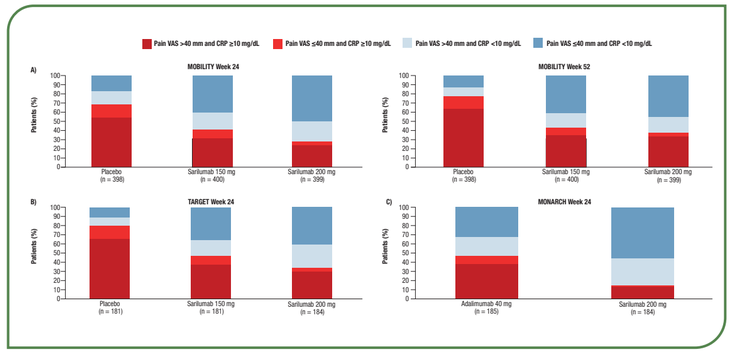
Analysis

- *Post-hoc* analyses were conducted on the following:
  - Odds ratios (ORs) of two pain outcomes:
    - **Unacceptable pain** (based on patient acceptable symptom state on a threshold of visual analog scale (VAS) pain >40 mm [0–100])[5]
    - **Refractory pain despite inflammation control** (unacceptable pain + C-reactive protein [CRP] <10 mg/L)[6,7]
    - **Refractory pain-*strict*** (refractory pain + ≤1 swollen joint count [SJC])[6,7]
  - Associations of pain and:
    - Fatigue (Functional Assessment of Chronic Illness Therapy [FACIT]-Fatigue)
    - Disease activity (Health Assessment Questionnaire Disability Index [HAQ-DI])
    - SJC
    - Tender joint count (TJC)
  - Agreements on the likelihood of achieving response (minimal clinically important differences [MCIDs]) on all these outcomes, based on the *Kappa* coefficient test on interrater reliability[8]

RESULTS

- Baseline characteristics were similar among study arms in each of the three RCTs
- Descriptive analysis of pain outcomes:
  - Across all three RCTs, sarilumab 150 mg and 200 mg were associated with better inflammation control and lower rates of unacceptable painversus comparators (**Figure 1**)
- Odds of unacceptable pain:
  - Across all three RCTs, sarilumab 150 mg and 200 mg had lower odds of unacceptable pain versus comparators with ORs (**Figure 2A**):
    - MOBILITY, Week 24 sarilumab 150 mg: 0.46 [0.34, 0.61]; sarilumab 200 mg: 0.39 [0.29, 0.52]) and Week 52 (sarilumab 150 mg: 0.40 [0.30, 0.54]; sarilumab 200 mg: 0.39 [0.30, 0.53]; all nominal $P < 0.001$
    - TARGET, sarilumab 150 mg: 0.41 [0.26, 0.65]; sarilumab 200 mg: 0.44 [0.28, 0.69]); nominal $P < 0.05$
    - MONARCH, sarilumab 200 mg: 0.54 [0.36, 0.81]; nominal $P < 0.05$
- Odds of refractory pain despite inflammation control:
  - In MOBILITY: both sarilumab doses had lower odds (nominal $P < 0.05$) of refractory pain versus placebo at Week 24 (sarilumab 150 mg: 0.60 [0.38, 0.93]; sarilumab 200 mg: 0.57 [0.37, 0.87]) and Week 52 (sarilumab 150 mg: 0.61 [0.37, 1.02]; sarilumab 200 mg: 0.62 [0.37, 1.02]; **Figure 2B**)
    - There were no significant differences in the odds of refractory pain for sarilumab 200 mg versus placebo or adalimumab 40 mg in TARGET and MONARCH, respectively
- Odds of refractory pain-*strict*:
  - In MOBILITY, both sarilumab doses had lower odds (nominal $P < 0.05$) of refractory pain-strict versus placebo at Week 52 (sarilumab 150 mg: 0.41 [0.19, 0.90]; sarilumab 200 mg: 0.35 [0.16, 0.76]; **Figure 2C**)
  - In TARGET, sarilumab 150 mg had lower odds (nominal $P < 0.05$) of refractory pain-*strict* at Week 24 (0.05 [0.01; 0.39]; **Figure 2C**)
  - In MONARCH, there was no significant difference in the odds of refractory pain-*strict* for sarilumab 200 mg versus adalimumab 40 mg

Figure 1. Descriptive analysis of unacceptable pain and inflammation control in A) MOBILITY (Week 24 and Week 52), B) TARGET, and C) MONARCH



CONCLUSIONS

- Joint pain could persist despite optimal inflammation control
- In this *post-hoc* analysis of three RCTs in patients who were inadequately responsive or intolerant to csDMARDs or TNFi with the given subsequent definitions of pain reduction, sarilumab was associated with lower odds of unacceptable pain or refractory pain versus placebo or adalimumab, with an acceptable safety profile
  - However when adjusting for complete control of inflammation (normalized CRP), patients who had longer duration of disease at study entry and/or had failed multiple csDMARDs or TNFi still had persisting pain, suggesting that prolonged inflammation over time was related to other causes of persisting pain
  - Moreover, in the MOBILITY RCT in which patients were followed to 52 weeks, only strict control of inflammation was associated with lower persistent pain at 52 weeks
- Further research is needed regarding the sources of persistent painand the potential role of inflammation control in patients with RAgiven that no significant differences were noted in two out of threestudies when evaluating pain despite inflammation control

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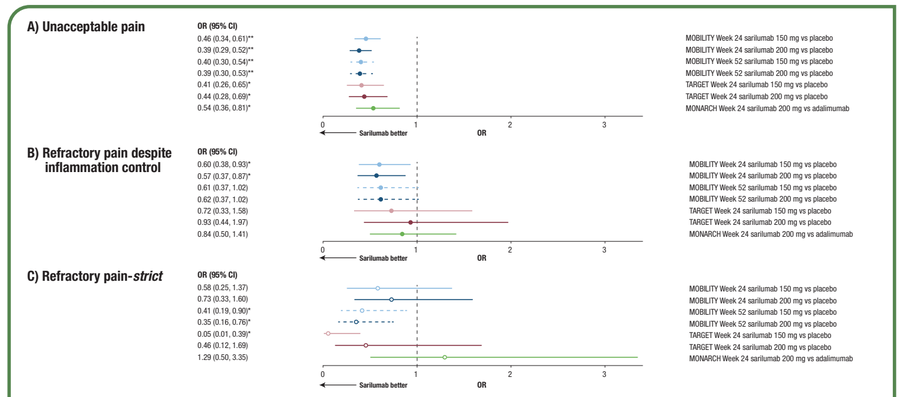
- Association of pain with FACIT-Fatigue, HAQ-DI, SJC, and TJC
  - Across all three RCTs, higher pain level was associated with worse levels of FACIT-Fatigue, HAQ-DI, SJC, and TJC (all $P < 0.001$)
  - Unacceptable pain had mostly moderate agreements with the likelihood of achieving response (MCID) on all these outcomes (*Kappa* coefficient values 0.41–0.60)

Figure 2. Odds ratios† for outcomes A) unacceptable pain, B) refractory pain despite inflammation control, and C) refractory pain-*strict*



Unacceptable pain: VAS pain >40 mm (0–100); Refractory pain (CRP <10 mg/L); Refractory pain-*strict*: Refractory pain + ≤1 SJC.

†The analyses were performed using the same model used for binary endpoints from each respective study stratified by geographical region and: prior TNFi use (TARGET), biologic DMARD use (MOBILITY), prior DMARD use (MONARCH).

**Nominal P < 0.0001; *nominal P < 0.05; 95% CI. MOBILITY: sarilumab SC 150 mg Q2W, sarilumab SC 200 mg Q2W versus placebo (+methotrexate for all). TARGET: sarilumab SC 150 mg Q2W, sarilumab SC 200 mg Q2W versus placebo (+csDMARDs for all). MONARCH: sarilumab SC 200 mg Q2W versus adalimumab SC 40 mg Q2W/QW.

CI, confidence interval.

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- Vivian Bykerk is a consultant for Sanofi and Regeneron Pharmaceuticals, Inc.
- Wenhui Wei and Toshio Kimura are employees and shareholders in Regeneron Pharmaceuticals, Inc.
- Susan Boklage was an employee and shareholder in Regeneron Pharmaceuticals, Inc. at the time of original presentation.
- Stefano Fiore is an employee and shareholder in Sanofi.
- Gregory St John was an employee of Regeneron Pharmaceuticals, Inc., may hold stock and/or stock options in the company, and is currently employed by Intercept Pharmaceuticals, Inc. and may hold stock and/or stock options in the company.

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